UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte MILAND RAJOPADHYE, D. SCOTT EDWARDS, THOMAS D. HARRIS, STUART J. HAMINWAY, SHUANG LIU, and PRAHLAD R. SINGH

Appeal 2007-0856
Application 09/281,474
Technology Center 1600

Decided: May 21, 2007

Before TONI R. SCHEINER, ERIC GRIMES, and LORA M. GREEN, *Administrative Patent Judges*.

GRIMES, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a compound comprising a targeting moiety and a chelator. The Examiner has rejected the claims for obviousness and obviousness-type double patenting. We have jurisdiction under 35 U.S.C. § 6(b). We affirm the obviousness rejection and reverse the obviousness-type double patenting rejection.

BACKGROUND

"Angiogenesis is the process by which new blood vessels are formed" (Specification 3). Angiogenesis is "an important component of a variety of physiological processes including ovulation, embryonic development, wound repair, and collateral vascular generation in the myocardium. It is also central to a number of pathological conditions such as tumor growth and metastasis, diabetic retinopathy, and macular degeneration." (*Id.*)

"Integrins are a diverse family of heterodimeric cell surface receptors by which endothelial cells attach to the extracellular matrix, each other and other cells" (*id.* at 4).

> The integrin $\alpha_v\beta_3$ is minimally expressed on normal blood vessels, but, is significantly upregulated on vascular cells within a variety of human tumors. The role of the $\alpha_v\beta_3$ receptors is to mediate the interaction of the endothelial cells and the extracellular matrix and facilitate the migration of the cells in the direction of the angiogenic signal, the tumor cell population.

(*Id.*)

The Specification describes compounds "comprised of a peptide or peptidomimetic targeting moiety that binds to a receptor that is upregulated during angiogenesis, . . . an optional linking group, . . . and a metal chelator" (*id.* at 8). The receptor may be $\alpha_v\beta_3$ (*id.* at 9-10).

"A 'chelator' . . . is the moiety or group on a reagent that binds to a metal ion through the formation of chemical bonds with one or more donor atoms" (*id.* at 57). "The metal chelator . . . is selected to form stable complexes with the metal ion chosen for the particular application. Chelators . . . for diagnostic radiopharmaceuticals are selected to form stable

complexes with the radioisotopes that have imageable gamma ray or positron emissions." (*Id.* at 75.) Chelators can also be selected to form therapeutic radiopharmaceuticals (*id.* at 80).

"The term 'peptide' . . . means "a linear compound that consists of two or more amino acids . . . that are linked by means of a peptide bond. . . . The term 'peptide' also includes compounds containing both peptide and non-peptide components, such as pseudopeptide or peptidomimetic residues or other non-amino acid components." (*Id.* at 59.) "A . . . 'peptidomimetic' is a compound which mimics the structure of an amino acid residue or a peptide, for example, by using linking groups other than amide linkages between the peptide mimetic and an amino acid residue (pseudopeptide bonds) and/or by using non-amino acid substituents and/or a modified amino acid residue" (*id.*). "The term 'amino acid' . . . means an organic compound containing both a basic amino group and an acidic carboxyl group" (*id.* at 58).

DISCUSSION

1. CLAIMS

Claims 1-10, 12-35, 48-50, 52, and 53 are pending and on appeal. We will focus on independent claims 1, 52, and 53, which are representative. The dependent claims subject to each rejection have not been separately argued and will therefore stand or fall with the claim on which they depend. 37 C.F.R. § 41.37(c)(1)(vii).

Claim 1 is reproduced in the Claims Appendix of Appellants' Brief, and is directed to a compound comprising a peptide or peptidomimetic $\alpha_v\beta_3$ receptor targeting moiety bound to a chelator. Claim 1 further recites that

the compound has a linking group of a specified formula between the targeting moiety and chelator. The Examiner correctly points out that the linking group recited in claim 1 can simply be, for example, O, S, C(=O), or an amino acid, where g, g', k, h', g'', h'', and g''' are all zero, as they can be (Answer 11).[1]

Claims 52 and 53 read as follows:

52. A compound comprising a peptide or peptidomimetic $\alpha_v\beta_3$ receptor targeting moiety bound to a chelator.

53. A compound, comprising a peptide or peptidomimetic $\alpha_v\beta_3$ receptor targeting moiety bound to a chelator, wherein said chelator is a diaminedithiol, monoamine-monoamidedithiol, triamide-monothiol, monoamine-diamide-monothiol, diaminedioxime, hydrazine, or cyclic polyaminocarboxylate, or acyclic polyaminocarboxylate.

2. REFERENCES

The Examiner relies on the following references:

Palladino	US 5,780,426	Jul. 14, 1998
Sharma	US 6,331,285 B1	Dec. 18, 2001
Harris	US 6,511,648 B2	Jan. 28, 2003
Cheesman	US 6,558,649 B1	May 6, 2003

3. OBVIOUSNESS

Claims 1, 2, 12-15, 17, 19-21, 25, 27, 28, 31-35, 48-50, 52, and 53 stand rejected under 35 U.S.C. § 103 as obvious over Palladino in view of Sharma. The Examiner relies on Palladino for disclosing "peptides that may be used to treat diseases involving αvβ3 receptors," including cancer and

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[1] In fact, when s, s', s'', t, and t' are also 0, it is unclear whether claim 1 requires a linking group at all.

angiogenic-based diseases (Answer 5). The Examiner argues that Palladino describes "non-RGD (RGD is the peptide sequence Arg-Gly-Asp) peptides that bind to the $\alpha_v\beta_3$ integrin receptor" (*id.*). The Examiner also argues that Palladino discloses that the "peptides may be labeled and discloses that a metal binding domain[] may be utilized. . . . [T]he phrase 'metal binding domains' is equivalent to 'chelators' in the art." (*Id.* at 9-10.) In addition, the Examiner argues that Palladino "disclose[s] that the labels are optionally attached by spacer arms of various lengths to reduce potential stearic [sic, steric] hindrance. . . . [T]he phrase 'spacer' is interchangeable with . . . 'linking group' in the art." (*Id.* at 10.)

The Examiner relies on Sharma for disclosing "peptide metalloconstructs that are useful for biological, therapeutic, diagnostic imaging, or radiotherapeutic purposes" (*id.* at 6). The Examiner argues that Sharma "is directed to peptides that . . . may be cyclic RGD mimics . . . , which are complexed with a metal ion binding backbone (chelator) and complexed with a metal" (*id.* at 10). The Examiner also argues that Sharma discloses that the peptide (i.e., the biological-function domain) is "distinct" from the metal binding backbone (*id.* at 7).

In addition, the Examiner argues that Sharma discloses "[v]arious chelators/ligands containing nitrogen, oxygen, and sulfur based coordination atoms . . . used to generate a tetradentate peptide construct. The tetradentate structure may be N4, N3S, N2S2, NS3, N2SO, or any similar combination yielding tetradentate coordination utilizing nitrogen, sulfur, and oxygen atoms." (*Id.*) In particular, the Examiner argues that N3S is the "same as [claim 53's] triami[d]e-monothiol or monoamine-diamide-monothiol

combination" and that N2S2 is the "same as [claim 53's] diaminedithiol or monoamine-monoamidedithiol combination" (*id.* at 11). The Examiner also argues that Sharma discloses "a peptide chain linked to a N3S containing chelator by a C(=O) spacer group" (*id.*).

The Examiner concludes that "one of ordinary skill in the art would be motivated to combine the teachings of Palladino et al and Sharma et al since both references are directed to peptides that may be labeled and contain a linking group" (*id.* at 10). "[W]hile Appellant[s] assert[] that the complexes of Sharma et al are conformationally constrained, the pending claims do not exclude conformationally constrained conjugates" (*id.*).

We conclude that the Examiner has set forth a prima facie case that claims 1, 52, and 53 would have been obvious. With regard to claim 52, Palladino describes a non-RGD peptide that binds to the $\alpha_v\beta_3$ integrin receptor and the use of this peptide for treating or detecting diseases involving this receptor (Palladino, col. 7, ll. 13-28). To diagnose disease, Palladino describes "determining the level of binding of the peptide to the $\alpha_v\beta_3$ integrin receptor. . . . To determine the level of binding, the peptide is labelled with a detectable label" (*id.* at col. 19, l. 61, to col. 20, l. 19). As a label, Palladino describes "polypeptide epitopes recognized by a secondary reporter," for example, "metal binding domains" (*id.* at col. 6, ll. 37-54). Based on the teachings of Palladino, we conclude that it would have been obvious to combine a metal binding domain, which constitutes a chelator as this term is used in the Specification, with the non-RGD peptide.

With regard to claim 53, Sharma describes a metallo-construct including "a metal ion-binding backbone for complexing with a metal ion,

and a biological-function domain" that is "conformationally constrained upon complexing the metal ion-binding backbone with the metal ion" (Sharma, col. 10, ll. 8-15). The biological-function domain "may constitute a ligand capable of forming a member of a ligand and receptor pair" (*id.* at col. 10, ll. 45-48). The metal ion acts as a label (*id.* at col. 1, ll. 22-23). In particular, Sharma describes "a molecule which, upon complexing with a metal ion, includes a biological-function domain which is specific for one or more of the RGD-binding integrin family of receptors for use in diagnostics and therapeutic modalities" (*id.* at col. 20, ll. 17-21).

In addition, Sharma describes a metal ion-binding backbone including a plurality of amino acids having nitrogen, sulfur, or oxygen atoms available to complex the metal ion (*id.* at col. 10, ll. 28-35). The preferred backbone is "based on the requisite number of particular coordinating groups required by the coordination sphere of a given complexing metal ion" (*id.* at col. 27, ll. 12-15). "Coordinating groups in the peptide chain include nitrogen atoms of amine, [or] amide . . . ; [and] sulfur atoms of thiols" (*id.* at col. 27, ll. 21-23). Specifically, Sharma describes a tetradentate peptide construct of, e.g., N_3S or N_2S_2 (*id.* at col. 27, ll. 30-42). Based on the teachings of Sharma, we agree with the Examiner that it would have been obvious to include a diaminedithiol, a monoamine-monoamidedithiol, a triamide-monothiol, or a monoamine-diamide-monothiol as the metal binding domain of Palladino.

With regard to claim 1, Palladino discloses that the labels may be "attached by spacer arms of various lengths to reduce potential stearic [sic, steric] hindrance" (Palladino, col. 6, ll. 54-55). In addition, Sharma depicts a metallopeptide having a C(=O) between the metal ion-binding backbone

and the biological-function domain (Sharma, col. 39, ll. 50-61). As discussed above, claim 1 encompasses a compound with a spacer consisting of C(=O). Thus, we agree with the Examiner that it would have been obvious to include a linking group within the formula recited in claim 1 between the non-RGD peptide and the metal binding domain of Palladino to reduce potential steric hindrance.

Appellants argue that Palladino "lacks a chelator, or in the alternative, lacks the limitation of the 'targeting moiety **bound to a chelator**'" (Br. 5). In particular, Palladino refers to "immunological labeling techniques as opposed to chelators" (*id.*).

We are not persuaded by this argument. Although Palladino also describes labeling techniques that do not involve chelators, we agree with the Examiner that Palladino describes a targeting moiety bound to a chelator for the reasons discussed above.

Appellants also argue that Sharma "relates to conformationally fixed peptides and metallo-constructs that have a metal ion binding backbone. . . . A metal is attached to O, N, or S, atoms present in the backbone or side chains of the peptide. Thus, Sharma also fails to teach a 'targeting moiety **bound to**' a chelator.'" (Br. 6.) "In fact, in col. 39, the Sharma reference states '[i]n these constructs a metal binding site is introduced **between** two pre-selected ends of a linear **peptide that contains the biological function domain**.' . . . If the peptide targeting moiety ***is*** the chelator, it's not 'bound to' the chelator." (*Id.*) "Therefore, even when combined, the references fail to teach all limitations of the claims" (*id.*)

In addition, Appellants argue that the references do not provide motivation to combine them. Palladino "has a **non-RGD** targeting moiety that does not appear to be conformationally fixed. In contrast, the Sharma reference has a **conformationally fixed RGD** containing peptide." (Br. 7.)

> If one skilled in the art removed the 'conformationally fixed' portion of the Sharma reference, the metal binding ability would be lost, thus, there is no motivation. On the other hand, the Examiner has cited no evidence that the Palladino reference's **non-RGD** targeting moiety could be conformationally fixed and retain activity. If it causes the targeting moiety to lose activity, the modification would be unsatisfactory for its intended purpose.

(*Id.*)

We are not persuaded by these arguments. First, these arguments do not apply to claim 52 because claim 52 would have been obvious in view of Palladino alone, as discussed above.

With regard to claims 1 and 53, we disagree with Appellants' argument that Sharma does not describe a targeting moiety bound to a chelator. As pointed out by the Examiner, Sharma discloses that the biological-function domain may be "distinct from the metal binding backbone," that is, the two domains "can be differentiated in the molecule" (Sharma, col. 30, l. 19, to col. 31, l. 1). Thus, Sharma describes a compound in which the biological-function domain, which can be a targeting moiety, is bound to the metal binding backbone (i.e., chelator).

We also disagree with Appellants' argument that there would have been no motivation to combine Palladino with Sharma. The relevant question is "whether there was an apparent reason to combine the known

elements in the fashion claimed by the patent at issue." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. __, __, 82 USPQ2d 1385, 1396 (2007).

Here, we agree with the Examiner that it would have been obvious to one of ordinary skill in the art to include the metal-ion binding backbones described in Sharma as the metal binding domain of Palladino. Although Sharma describes including these metal-ion binding backbones in a structure that conformationally fixes the biological-function domain, Appellants have provided no evidence that including these metal-ion binding backbones to label the non-RGD peptide of Palladino would cause the non-RGD peptide to lose activity. In addition, we agree with the Examiner that one of ordinary skill in the art would have included a linking group, such as the C(=O) depicted in Sharma, between the non-RGD peptide and the metal binding domain of Palladino in order to reduce potential steric hindrance.

With regard to claim 1, Appellants argue that Palladino "states that '[i]n some embodiments, labels are attached by spacer arms of various lengths to reduce potential stearic hindrance.' . . . However, the labels are not chelators, and thus the limitation of 'a linking group between the targeting moiety and chelator' cannot be met." (Br. 8.) Appellants also argue that the Examiner "failed to analyze how one skilled in the art, armed with the Palladino reference's single disclosure of 'spacer arms' (found *solely* at col. 6, lines 54-55) would arrive at Appellants['] claimed formula" (*id.*).

We are not persuaded by these arguments. First, we find that Palladino describes labels that are chelators for the reasons discussed above. Second, although Palladino does not describe the structure of its spacer

arms, we conclude that spacer arms within the linking group formula of claim 1 would have been obvious for the reasons discussed above.

We conclude that the Examiner has set forth a prima facie case that claims 1, 52, and 53 would have been obvious over Palladino in view of Sharma, which Appellants have not rebutted. We therefore affirm the rejection of claims 1, 52, and 53 under 35 U.S.C. § 103. Claims 2, 12-15, 17, 19-21, 25, 27, 28, 31-35, and 48-50 depend from and therefore fall with claim 1.

4. OBVIOUSNESS-TYPE DOUBLE PATENTING

Claims 1-10, 12-35, 48-50, 52, and 53 stand rejected under the judicially-created doctrine of obviousness type double patenting over the claims of Harris and Cheesman. The Examiner argues that the present claims are not patentably distinct from the claims of Harris and Cheesman because both the present claims and the patented claims "are directed to a targeting moiety, chelator, peptide/non-peptide, optionally a metal, and optionally, a linker" (Answer 3 and 4). Although the claims of Harris and Cheesman recite that the targeting moiety is a non-peptide, the Examiner argues that

> the term 'non-peptide' means preferably less than three amide bonds in the backbone core of the targeting moiety or ***preferably less than three amino acids or amino acid mimetics in the targeting moiety*** (see . . . [Cheesman], column 28, lines 14-17; . . . and [Harris], column 67, lines 6-9). In the instant invention, . . . the term 'peptide' is defined as a linear compound that ***consists of two or more amino acids*** that are linked by means of a peptide bond. In addition, Appellant[s] disclose[] that the term 'peptide' also includes compounds containing both peptide and non-peptide components such as pseudopeptide or peptidomimetic residues or other non-amino

> acid components. Thus, Appellant[s'] use of the term 'peptide' encompasses both peptide and non-peptide targeting moieties.

(*Id.* at 9.)

Appellants argue that Harris "relates to a compound, comprising a targeting moiety and a chelator, *wherein the targeting moiety is a quinolone nonpeptide.* In contrast, the Appellants['] claims recite that *the targeting moiety is a 'peptide or peptidomimetic.'*" (Br. 10.) Similarly, Appellants argue that Cheesman "relates to a compound, comprising a targeting moiety and a chelator, wherein *the targeting moiety is a benzodiazepine nonpeptide.* In contrast, the Appellants['] claims recite that the *targeting moiety is a 'peptide or peptidomimetic.'*" (Br. 11.)

We conclude that the Examiner has not set forth a prima facie case that the claims of Harris and Cheesman are patentably indistinct from the instant claims. As noted by Appellants, claim 1 of Harris and Cheesman recite a targeting moiety that is a quinolone nonpeptide and a benzodiazepine nonpeptide, respectively. Identifying the targeting moiety as a quinolone nonpeptide or a benzodiazepine nonpeptide indicates that a quinolone or a benzodiazepine that is not part of a peptide can be used to target the receptor. Granted, Harris and Cheesman define the term "nonpeptide" as meaning "preferably less than three amide bonds in the backbone core of the targeting moiety or preferably less than three amino acids or amino acid mimetics in the targeting moiety" (Harris, col. 67, ll. 6-10; Cheesman, col. 28, ll. 14-17). However, we do not agree with the Examiner that the recitation of a quinolone nonpeptide or a benzodiazepine nonpeptide targeting moiety suggests a targeting moiety that is a peptide, even if the peptide can include non-peptide components.

Thus, we do not agree that the Examiner has set forth a prima facie case that the patented compounds, comprising a quinolone nonpeptide or a benzodiazepine nonpeptide, are not patentably distinct from the instantly claimed compounds, comprising a peptide or peptidomimetic targeting moiety. We therefore reverse the obviousness-type double patenting rejection of claims 1-10, 12-35, 48-50, 52, and 53.

OTHER ISSUE

As discussed in footnote 1, there is arguably some ambiguity as to whether claim 1 necessarily requires a linking group. If prosecution of this case is continued, this ambiguity should be resolved.

SUMMARY

We affirm the rejection of claims 1, 2, 12-15, 17, 19-21, 25, 27, 28, 31-35, 48-50, 52, and 53 under 35 U.S.C. § 103. However, we reverse the rejection of claims 1-10, 12-35, 48-50, 52, and 53 for obviousness-type double patenting. Thus, claims 3-10, 16, 18, 22-24, 26, 29, and 30 are not currently subject to a rejection.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED-IN-PART

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BRISTOL – MYERS SQUIBB COMPANY
PATENT DEPARTMENT
PO BOX 4000
PRINCETON NJ 08543-4000